Human genetic variation within neural crest enhancers: molecular and phenotypic implications.

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Public Summary:

Scientific Abstract:
Developmental gene expression programmes are coordinated by the specialized distal cis-regulatory elements called enhancers, which integrate lineage- and signalling-dependent inputs to guide morphogenesis. In previous work, we characterized the genome-wide repertoire of active enhancers in human neural crest cells (hNCC), an embryonic cell population with critical roles in craniofacial development. We showed that in hNCC, co-occupancy of a master regulator TFAP2A with nuclear receptors NR2F1 and NR2F2 correlates with the presence of permissive enhancer chromatin states. Here, we take advantage of pre-existing human genetic variation to further explore potential cooperation between TFAP2A and NR2F1/F2. We demonstrate that isolated single nucleotide polymorphisms affecting NR2F1/F2-binding sites within hNCC enhancers can alter TFAP2A occupancy and overall chromatin features at the same enhancer allele. We propose that a similar strategy can be used to elucidate other cooperative relationships between transcription factors involved in developmental transitions. Using the neural crest and its major contribution to human craniofacial phenotypes as a paradigm, we discuss how genetic variation might modulate the molecular properties and activity of enhancers, and ultimately impact human phenotypic diversity.